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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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DAVID R PRESTON & ASSOCIATES
12625 HIGH BLUFF DRIVE
SUITE 205
SAN DIEGO, CA 92130

EXAMINER	
TAYLOR, JANELL E	
ART UNIT	PAPER NUMBER
1634	10

DATE MAILED: 06/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,621	RAUCY, JUDY	
	Examiner	Art Unit	
	Janell Taylor	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 2 recites the limitation "said enzyme involved in drug metabolism". There is insufficient antecedent basis for this limitation in the claim, as it depends from claim 1, and the word "enzyme" is not found in that claim.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. Claims 1, 3, 4, 9, 11,14-17, 19, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Lohray et al. (USPN 6,054,453, filed January 23, 1998).

Lohray et al teaches tricyclic compounds and their use in medicine, the process for their preparation and pharmaceutical compositions containing them. Lohray teaches an example whereby the efficacy of two pharmaceutical compounds was tested. "Ligand binding domain of hPPAR alpha was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPAR alpha was measured using Packard Luclite kit (Packard, USA)." Therefore, Lohray teaches a cell comprising two plasmids. The first plasmid, or nucleic acid, contains a ligand binding domain fused to DNA binding domain of yeast transcription factor GAL4. (This corresponds to the second nucleic acid of the instant claims, in which a nucleic acid encoding a transcription factor, which is associated with or activated by a compound, is claimed.) The second nucleic acid taught by Lohray is a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. (This corresponds to the first nucleic acid taught by the instant claims: a promoter operably linked to a reporter). Lohray also teaches that the cell is contacted with a compound that induces expression of the protein involved in drug metabolism, and the reporter gene is expressed. The GAL4 is a protein involved in drug metabolism, and the test compound induces the expression of GAL4, which in turn causes the expression of the reporter (luciferase.) Lohray also teaches the reporter is an enzyme, luciferase

(corresponding to claim 3). Lohray also teaches that the nucleic acid molecule is present as an extrachromosomal element (both the first and second nucleic acid molecule, which corresponds to claims 4 and 11). Lohray also teaches that transcription factor (GAL4) forms a complex with the drug and produces transcriptional activation of a gene encoding a protein involved in drug metabolism. (Corresponds to instant claim 9). The transfected cell is a HEK-293 cell, which is a human embryonic kidney cell. (Corresponds to instant claims 14-18). Lohray also teaches a method for evaluating compounds for the property of inducing expression of a gene by providing a test compound, contacting the test compound with the cell, and detecting the expression of the reporter gene. (Corresponds to instant claim 19). Furthermore, the method may be considered high throughput, as it is possible using the method to carry out upwards of five assays a day. (Claim 20).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray as applied to claim 1 above, and further in view of Luskey et al (USPN 6,262,118).

As disclosed above, Lohray teaches tricyclic compounds and their use in medicine, the process for their preparation and pharmaceutical compositions containing

them. Lohray teaches an example whereby the efficacy of two pharmaceutical compounds was tested. "Ligand binding domain of hPPAR alpha was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPAR alpha was measured using Packard Luclite kit (Packard, USA)." Therefore, Lohray teaches a cell comprising two plasmids. The first plasmid, or nucleic acid, contains a ligand binding domain fused to DNA binding domain of yeast transcription factor GAL4. (This corresponds to the second nucleic acid of the instant claims, in which a nucleic acid encoding a transcription factor, which is associated with or activated by a compound, is claimed.) The second nucleic acid taught by Lohray is a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. (This corresponds to the first nucleic acid taught by the instant claims: a promoter operably linked to a reporter). Lohray also teaches that the cell is contacted with a compound that induces expression of the protein involved in drug metabolism, and the reporter gene is expressed.

Lohray does not, however, teach that the enzyme involved in drug metabolism is selected from the group consisting of P450s, glucoronosyl transferases, N-acetyltransferases, p-glycoproteins, glutathione transferases and sulfo transferases.

Luskey et al. teach that there were indications of drug-drug interactions of racemic halofenate with agents such as Coumadin. Coumadin is an anticoagulant that acts by inhibiting the synthesis of Vitamin K dependent clotting factors. Coumadin is believed to be stereospecifically metabolized by hepatic microsomal enzymes (the cytochrome P450 enzymes). The cytochrome P450 enzymes involved in the metabolism of Coumadin are likely to be the principal form of human liver P450 which modulates in vivo drug metabolism of several drugs including Coumadin.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Lohray with that of Luskey. It would have been obvious for the protein involved in drug metabolism of claim 1 to be P450. This is because, as taught by Luskey, it was known that the cytochrome P450 enzymes were involved in the metabolism of certain drugs, such as Coumadin. It would have been obvious to carry out an assay using the cell of claim 1, where the protein involved in drug metabolism was P450, because it would have allowed one of ordinary skill in the art to determine the role of P450 in drug metabolism.

5. Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray, as applied to claim 1 above, and further in view of Foulkes et al (USPN 5,976,793).

As disclosed above, Lohray teaches tricyclic compounds and their use in medicine, the process for their preparation and pharmaceutical compositions containing them. Lohray teaches an example whereby the efficacy of two pharmaceutical compounds was tested. "Ligand binding domain of hPPAR alpha was fused to DNA

binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPAR alpha was measured using Packard Luclite kit (Packard, USA)." Therefore, Lohray teaches a cell comprising two plasmids. The first plasmid, or nucleic acid, contains a ligand binding domain fused to DNA binding domain of yeast transcription factor GAL4. (This corresponds to the second nucleic acid of the instant claims, in which a nucleic acid encoding a transcription factor, which is associated with or activated by a compound, is claimed.) The second nucleic acid taught by Lohray is a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. (This corresponds to the first nucleic acid taught by the instant claims: a promoter operably linked to a reporter). Lohray also teaches that the cell is contacted with a compound that induces expression of the protein involved in drug metabolism, and the reporter gene is expressed.

Lohray does not, however, teach that the first nucleic acid (the reporter and promoter nucleic acid) is within the chromosome of the cell, or that the promoter is endogenous to the chromosome.

Foulkes et al teach methods of transcriptionally modulating gene expression and of discovering chemicals capable as gene expression modulators. Specifically, they teach "The invention provides that the reporter gene in the DNA contained in the cell

sample, which expresses a polypeptide capable of producing a detectable signal coupled to, and under control of, the promoter, may be inserted downstream of the endogenous promoter of the gene-of-interest by homologous recombination. The following provides a method of determining whether a molecule not previously known to be a modulator of protein biosynthesis is capable of transcriptionally modulating the expression of a gene-of-interest which comprises contacting a sample which contains a predefined number of cells with a predetermined amount of a molecule to be tested, each such cell comprising DNA consisting essentially of (i) a modulatable transcriptional regulatory sequence of the gene-of-interest, (ii) a promoter of the gene-of-interest, and (iii) a DNA sequence transcribable into mRNA coupled to and under the control of, the promoter, under conditions such that the molecule, if capable of acting as a transcriptional modulator of the gene-of-interest, causes a measurable difference in the amount of mRNA transcribed from the DNA sequence, quantitatively determining the amount of the mRNA produced, comparing the amount so determined with the amount of mRNA detected in the absence of any molecule being tested or upon contacting the sample with any other molecule, and thereby identifying the molecule as one which causes a change in the detectable mRNA amount of, and thus identifying the molecule as a molecule capable of transcriptionally modulating the expression of the gene-of-interest. In one example of the above-described method, the molecule (a) does not naturally occur in the cell, (b) specifically transcriptionally modulates expression of the gene-of-interest, and (c) binds to DNA or RNA or binds to a protein through a domain of such protein which is not a ligand binding domain of a receptor which naturally occurs in

the cell, the binding of a ligand to which ligand binding domain is normally associated with a defined physiological or pathological effect." (Col. 27). Therefore, Foulkes teaches a reporter gene which is inserted into the chromosome of a cell, downstream of an endogenous promoter. Foulkes further teaches carrying out an assay in which the reporter gene is used to determine transcriptional modulation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Lohray with that of Foulkes. This is because it would have been obvious to use an endogenous promoter, as this would have allowed for the naturally occurring promoter to be assayed, which would have provided valuable information as to the functionality of the endogenous promoter. Furthermore, it would have been obvious to insert a reporter downstream of the promoter, as it would have allowed one of ordinary skill in the art at the time of the invention to assay for the activity of the promoter. Furthermore, it would have allowed the detection of translation, regulated by the promoter, in the absence of a naturally occurring polypeptide which may have functioned as a reporter.

6. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray et al as applied to claim 1 above, and further in view of Boeke et al. (USPN 5,840,579).

As disclosed above, Lohray teaches tricyclic compounds and their use in medicine, the process for their preparation and pharmaceutical compositions containing them. Lohray teaches an example whereby the efficacy of two pharmaceutical compounds was tested. "Ligand binding domain of hPPAR alpha was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector.0

Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPAR alpha was measured using Packard Luclite kit (Packard, USA)." Therefore, Lohray teaches a cell comprising two plasmids. The first plasmid, or nucleic acid, contains a ligand binding domain fused to DNA binding domain of yeast transcription factor GAL4. (This corresponds to the second nucleic acid of the instant claims, in which a nucleic acid encoding a transcription factor, which is associated with or activated by a compound, is claimed.) The second nucleic acid taught by Lohray is a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. (This corresponds to the first nucleic acid taught by the instant claims: a promoter operably linked to a reporter). Lohray also teaches that the cell is contacted with a compound that induces expression of the protein involved in drug metabolism, and the reporter gene is expressed.

Lohray does not, however, teach that the reporter gene is endogenous to the chromosome of the cell.

Boeke teaches the use of an endogenous reporter gene (Col. 7, bridging Col. 8).

It would have been obvious to one of ordinary skill in the art at the time of the invention that the reporter gene of Lohray may have been endogenous. This is because it would have been useful to use an endogenous reporter gene, as it would have allowed the naturally occurring product of an assay to be detected. Furthermore, it

would have reduced manipulation of the cell that was being assayed, which would have resulted in clearer results.

7. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray et al, as applied to claim 1 above, and further in view of Klein (USPN 6,255,959).

As disclosed above, Lohray teaches tricyclic compounds and their use in medicine, the process for their preparation and pharmaceutical compositions containing them. Lohray teaches an example whereby the efficacy of two pharmaceutical compounds was tested. "Ligand binding domain of hPPAR alpha was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPAR alpha was measured using Packard Luclite kit (Packard, USA)." Therefore, Lohray teaches a cell comprising two plasmids. The first plasmid, or nucleic acid, contains a ligand binding domain fused to DNA binding domain of yeast transcription factor GAL4. (This corresponds to the second nucleic acid of the instant claims, in which a nucleic acid encoding a transcription factor, which is associated with or activated by a compound, is claimed.) The second nucleic acid taught by Lohray is a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. (This corresponds to the first nucleic acid taught by the instant claims: a promoter operably linked to a reporter). Lohray also teaches that the cell is

contacted with a compound that induces expression of the protein involved in drug metabolism, and the reporter gene is expressed.

Lohray does not specifically teach that the second molecule (the transcription factor) is an orphan receptor or a hormone receptor.

Klein teaches methods for identifying G protein coupled receptor effectors. Specifically, Klein teaches that the sequencing of seven transmembrane domain G receptors led to the discovery of a large number of orphan receptors. Klein teaches that "The importance of identifying ligands for orphan receptors is clear; it opens up a wide area for research in the area of drug discovery." (Col. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention that the transcription factor may have been an orphan receptor. As Klein teaches, many were known in the art, and it would have been useful to use them in drug discovery assays, as they would have provided valuable information on the drug interactions that take place in a cell.

8. Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray as applied to claim 1 above, and further in view of Sherr et al. (USPN 6,303,772).

As disclosed above, Lohray teaches tricyclic compounds and their use in medicine, the process for their preparation and pharmaceutical compositions containing them. Lohray teaches an example whereby the efficacy of two pharmaceutical compounds was tested. "Ligand binding domain of hPPAR alpha was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector.

Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPAR alpha was measured using Packard Luclite kit (Packard, USA)." Therefore, Lohray teaches a cell comprising two plasmids. The first plasmid, or nucleic acid, contains a ligand binding domain fused to DNA binding domain of yeast transcription factor GAL4. (This corresponds to the second nucleic acid of the instant claims, in which a nucleic acid encoding a transcription factor, which is associated with or activated by a compound, is claimed.) The second nucleic acid taught by Lohray is a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. (This corresponds to the first nucleic acid taught by the instant claims: a promoter operably linked to a reporter). Lohray also teaches that the cell is contacted with a compound that induces expression of the protein involved in drug metabolism, and the reporter gene is expressed.

Lohray does not teach that the transcriptional factor is present within the chromosome of the cell, or that it is endogenous to the chromosome of the cell.

Sherr teaches cyclin D binding factor, and uses thereof. In particular, Sherr teaches "Another aspect of the present invention includes methods of activating selective transcription of a heterologous gene operably associated with a DNA sequence to which the present transcription factor binds in mammalian cells...In some embodiments of the invention, the endogenous transcription factor of the invention in

the mammalian cell will be sufficient to activate selective transcription of the heterologous gene." (Col. 7). Therefore, Sherr teaches the use of an endogenous transcription factor to activate selective transcription of a heterologous gene.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Lohray with those of Sherr. This is because Sherr taught that using an endogenous transcription factor would have been sufficient to activate selective transcription of a gene. It would have been useful for the transcription factor of the present invention to have been endogenous to the chromosome, as it would have allowed for the endogenous transcription factor to be assayed in the cell in which it naturally resides, which would have aided in drug discovery as it would have given valuable information as to the function of the endogenous transcription factor.

Summary

Claim 2 is rejected under 35 U.S.C. 112, second paragraph. Claims 1, 3, 4, 9, 11, and 14-20 are rejected under 35 U.S.C. 102(e). Claims 2, 5-8, 10, and 12-13 are rejected under 35 U.S.C. 103(a). No claims are free of the prior art.

Conclusion

Any inquiries of a general nature relating to this application, including information on IDS forms, status requests, sequence listings, etc. should be directed to the Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 872-9306 or 872-9307 (after final). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

June 12, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600